投稿 ▶原著

既承認核酸医薬品の組織分布及び血漿/血清タンパク結合評価に関する調査と考察

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Survey and Consideration for Evaluation of Tissue Distribution and Plasma/Serum Protein Binding Properties of Approved Oligonucleotide Therapeutics

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Summary

In recent years, the clinical development of oligonucleotide therapeutics, such as antisense oligonucleotide (ASO) and small interfering RNA (siRNA), has been active. Applications for regulatory approval require a series of assessments of the absorption, distribution, metabolism, excretion, and drug-drug interaction characteristics of these oligonucleotide therapeutics using appropriate methods. It is particularly important to understand the tissue distribution and plasma/serum protein binding properties of oligonucleotide therapeutics in assessing their efficacy and safety. However, no comprehensive studies have been conducted to investigate how tissue distribution and protein binding are evaluated and what properties are determined as a result.

In this study, we examined the review reports for approved oligonucleotide therapeutics released by the regulatory authorities, as well as related papers to investigate the evaluation methods and the tissue distribution and plasma/serum protein binding properties of the currently approved ASO and siRNA therapeutics.

First, quantitative whole-body autoradiography (QWBA) studies using radiolabeled compounds were in principle conducted for the evaluation of tissue distribution throughout the whole body, as is the case with small-molecule drugs. In many cases, distribution to tissues of particular interest, such as organs with a high distribution rate, was evaluated by a combination of methods, including liquid chromatography-mass spectrometry (LC-MS), capillary electrophoresis (CE), high-performance liquid chromatography (HPLC), hybridization enzyme-linked immunosorbent assay (ELISA), and hybridization electrochemiluminescence (ECL) after administration of unlabeled compounds. The results of these tissue distribution evaluations showed that systemically administered ASO therapeutics consisting solely of oligonucleotides were rapidly distributed throughout the body and were highly concentrated in the kidneys in all cases, regardless of animal species. In contrast, all the siRNA therapeutics were highly directed to the liver, and GalNAc-siRNA, in particular, tended to accumulate predominantly in the liver, the therapeutic target tissue.

The plasma/serum protein binding of ASO therapeutics was evaluated by methods commonly used for small-molecule drugs such as ultrafiltration and ultracentrifugation, while gel-shift assay was also used for siRNA therapeutics as a new evaluation method. As regards the protein binding properties of the ASO therapeutics, the plasma/serum protein binding rate of morpholino ASOs was generally low (40％ or less), whereas the plasma protein binding rate of phosphorothioate ASOs was 85％ or more. In contrast, for siRNA therapeutics, LNP-siRNA showed a low serum protein binding rate of approximately 2％ or less, whereas the plasma protein binding rate in GalNAc-siRNAs at concentrations around the clinical exposure level was 76％ or higher in human.

The tissue distribution and protein binding of oligonucleotide therapeutics are particularly sensitive to the molecular structure of oligonucleotides and the drug delivery system (DDS) technology employed, so an accurate understanding of these properties is important for the development of oligonucleotide therapeutics. This survey revealed that new evaluation methods for tissue distribution and protein binding were employed in addition to conventional evaluation methods, and indicated that these methods provided an improved understanding of the tissue distribution and protein binding properties.

Key words

Antisense oligonucleotide, Small interfering RNA, Tissue distribution, Protein binding